

In The Claims

Please amend claims 11,12,13 and 18 as rewritten in the clean version of the entire set of pending claims shown in Appendix A (attached hereto). A marked-up version of the rewritten claims is shown in Appendix B (attached hereto).

REMARKS

Application Status

Claims 1-24 were pending in the subject application. Upon entry of this amendment, claims 11,12,13 and 18 will have been amended. Claims 11,12,and 13 were amended to identify the degenerative condition of claim 1. Therefore claims 1-24 remain before the Examiner for consideration.

Rejection Under 35 U.S.C. §102 (b)

In the Office Action, claims 1, 2, 5 and 18 were rejected under 35 U.S.C. §102(b) as being anticipated by Wheeler. Specifically, the Office Action stated that:

Claims 1,2,5 and 18 are rejected under 35 U.S.C. 102 (b) as being anticipated by Wheeler et al.. Wheeler et al. teach the use [of] brimonidine in a pharmaceutical formulation for the prevention of damage to the retinal (sic). The above reference makes clear that the claimed composition and the use thereof is old and well known. Such composition is inherently kept in a pharmaceutically acceptable kit. The kit of the claimed invention in the absence of any unusual feature reads on the kit taught by the prior art. The use of a label or instruction on a kit does not create a patentably distinct kit.

Applicants note that Wheeler discloses the use of brimonidine in a pharmaceutical formulation. However the composition described in Wheeler is used completely differently from that of the claimed invention.

As illustrated in Fig. 1 of the Application and described in §4.3 of the Specification (p. 12), the retina is a multi-layered structure composed of discrete layers of highly differentiated classes of neurons, with uniquely specialized functions in the visual process. The objective of Applicants' invention is preservation of structural and functional integrity of *photoreceptors*, which make up the outermost layer of retinal neurons, and are responsible for the initial detection of photons of light by the retina. By contrast, Wheeler describes the use of brimonidine to effect protection only of *retinal ganglion cells* (RGCs), cells situated on the opposite, i.e. inner, surface of the retina. RGCs function as traditional neurons, transmitting nerve impulses received from several classes of neurons within the retina to neurons in the brain. Transmission to the brain is carried by the axons of the RGCs, which converge on the inner aspect of the retina to form the optic nerve, which exits the eye and ultimately relays information to the visual centers in the brain.

As a further distinction between photoreceptors and RGCs, the blood supply to the inner retina, where the RGCs are situated, is completely separate from that of the photoreceptors. The inner retina is nourished by branches of the retinal artery whereas the photoreceptors have no blood supply of their own, relying on transfer of nutrients from the choroidal vasculature, which underlies the retinal pigmented epithelium (RPE). From the foregoing it is clear that structurally, functionally and spatially, photoreceptors and RGCs are widely disparate classes of cells within the retina.

Given the extreme differences in location and function of the two classes of cells, one of ordinary skill in the art would not predict that factors promoting survival of RGCs would have any beneficial effect on photoreceptors. This issue is neither addressed nor considered in Wheeler. Wheeler describes two methods of neuronal insult to RGCs—optic nerve crush and retinal ischemia—to study survival of RGCs in the presence or absence of brimonidine compositions. Photoreceptors are not even mentioned in Wheeler.

As discussed above and in the Specification, pp 12-13, in addition to their completely different functions, the two classes of retinal neurons are widely separated spatially and are nourished by separate blood supplies. Accordingly, diseases and injuries that affect RGCs do not harm photoreceptors, and vice versa. For example, in optic nerve damage causing RGC degeneration, studies (discussed in the Specification, p. 12, line 30) have shown that despite blindness rendered by complete sectioning of the optic nerve, photoreceptor function is unaffected in the retinas of the blinded animals. Similarly, ischemia of the inner retina, induced by ligation of the retinal artery, has no effect on the physiological response detectable from the photoreceptors.

Particularly convincing evidence of the physiological independence of the RGCs from the photoreceptors may be found in results of elegant electrophysiological experiments involving the use of isolated mammalian eyes maintained in a carefully controlled *in vitro* system. A description of such studies may be found in a recent review article by Niemeyer (2001), a copy of which is attached for the Examiner's convenience and is marked as Exhibit "A". Relevant sections of the article have been highlighted in

yellow for convenience. See Fig. 1, p.291 of Exhibit "A" for an illustration of the Niemeyer experimental system.

As discussed in Niemeyer, the functional responses of the multiple classes of neurons within the retina may be distinguished with great specificity by the technique of electroretinography (ERG). The characteristic electrical responses of particular classes of retinal neurons, displayed as trace recordings on the ERG, have been well studied for many years. Of particular relevance to the present discussion, the responses of the RGCs, and the related optic nerve (ON) action potential can be detected (see Exhibit "A" Fig. 4, p. 297), and clearly distinguished from the "b-wave" of the ERG, which is an electrical response driven by the photoreceptors.

Turning now to Table 3 of Niemeyer, p.313, one sees a list of six different conditions experimentally induced in eyes, with a comparison of the effects of each condition on the ERG responses of the RGCs (indicated by "ONR ON- amplitude") and the photoreceptors (indicated by "b-wave amplitude"). From review of this table, and particularly the column indicated "Comment," it is clear that under each experimentally induced condition, the electrophysiological responses of the photoreceptors and RGCs were markedly different.

For the above reasons, Applicants respectfully contend that their use of brimonidine compounds for treatment of photoreceptors is novel and not anticipated by Wheeler. Rejected claims 1, 2, and 5 all include limitations neither claimed nor disclosed by Wheeler. In particular, claim 1, claim 2 dependent thereon, and claim 5 are all directed to "a method of inhibiting a degenerative condition of a retinal photoreceptor cell" (or "retinal photoreceptors"). Wheeler is silent as to photoreceptors; thus it does not teach

all of the limitations of claims 1 and 5, nor therefore of any claim depending from claim 1 or 5. Accordingly, withdrawal of the rejection of claims 1, 2 and 5 is requested.

Claim 18, also rejected as anticipated under Wheeler, has been amended to include limitations not disclosed in Wheeler. In order to clarify and better define the distinction between Applicants' claims and Wheeler, amended claim 18 refers to "a brimonidine composition pharmaceutically suitable for topical administration to the eye and instructions for administration to a subject in need of treatment for *photoreceptor* degeneration."

Rejection Under 35 U.S. § 103

Claims 3-4, 6-17 and 19-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Wheeler et al., Sallman et al. (U.S. Patent No. 5,891,913) and Wen et al. (U.S. Patent 6,066,675).

The Office Action asserts that Wheeler et al. teach the protective effect of brimonidine on retinal photoreceptor cells, and that Sallman et al. teach the use of secondary active ingredients, wetting agents and ophthalmic carriers in an ophthalmic formulation for treatment of inflammatory conditions of the eye. It is asserted that the primary reference differs from the claimed invention in the presence of the secondary ingredients and ophthalmic carriers, and that it would have been obvious for a person skilled in the art to incorporate such teaching into the primary reference.

As explained above in the section relating to rejection under 35 U.S.C. § 102(a), the teaching of the primary reference, i.e. Wheeler et al., differs greatly from that of the claimed invention. Wheeler et al. teaches the use of brimonidine compounds exclusively

for the protection of retinal ganglion cells (RGCs), which are structurally, functionally and spatially widely disparate from photoreceptors. Sallman et al. primarily teaches the use of diclofenac potassium as a medicament for treatment of inflammatory conditions of the eye and discloses ophthalmic compositions containing diclofenac potassium and secondary agents such as carriers, solubilizers and stabilizers. However, as discussed above, Wheeler et al. provides no reason to expect that such a composition would have any effect on photoreceptors. Thus one skilled in the art would not have been motivated to combine the teachings of Wheeler et al. and Sallman et al. in attempting to develop an ophthalmic solution for treatment of photoreceptor degeneration. In fact, the motivation if any would have been to combine the teachings of Wheeler et al. and Sallman et al. in order to produce a brimonidine-based ophthalmic composition for treatment of ganglion cells.

Rejected claims 3 and 4 depend from claim 1, which as discussed above, provides a "method of inhibiting a degenerative condition of a retinal photoreceptor cell...." Similarly, rejected claims 6-13 depend from claim 5, which provides "a method of treating a degenerative condition of retinal photoreceptors...." The combined teachings of Wheeler et al. and Sallman et al. do not suggest the use of the claimed composition for treatment of photoreceptors and therefore do not teach all of the limitations of the claimed invention. Applicants respectfully request therefore that rejection of claims 3, 4 and 6-17 be withdrawn.

The Office Action asserts that "Wen et al. teach the use of growth factor for the treatment of retinal degeneration," and refers to the growth factor of claim 19 as an agent used for the treatment of retinal degeneration. The quotation from Wen et al. referenced

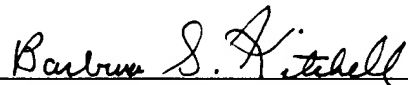
in the Office Action pertains to a disclosed method used "to stimulate growth factor mRNA transcription" (see Col. 4 line 18). The experiments described in Wen et al. involved the use of systemic injection of clonidine or xylazine to cause transient increased expression of the mRNA of a growth factor, i.e. basic fibroblast growth factor (bFGF), within the rat retina. Results by Northern blot analysis showed that bFGF expression was detectable in untreated and control rat tissues, but such expression was increased within whole retinas, but not brain tissues, following administration of clonidine or xylazine (see Wen et al., Figs. 1-3). Within the retinas, the increased bFGF expression was shown by in situ hybridization to be localized to the inner segments of the photoreceptors. Thus the effect of the systemic administration of xylazine or clonidine was to transiently increase the level of expression of bFGF that is intrinsic to the photoreceptor cells in the rat retina. Growth factors were not added to the compositions used in Wen.

Wen et al. do not teach the addition of externally applied bFGF or other growth factors as agents for treatment of retinal degeneration, but rather teach the use of xylazine and clonidine as agents to cause increased expression of the mRNA for bFGF, which is inherently expressed within the photoreceptor cells. To demonstrate the protective effect of such increased bFGF expression in photoreceptors subjected to stress, Wen et al. showed an increase in the rate of photoreceptor preservation in rats injected with xylazine or clonidine prior to exposure to high levels of light, a condition known to cause light-induced photoreceptor degeneration. There is no suggestion in Wen et al. that the application to the retina of *exogenous* growth factors such as bFGF or others could be used as a treatment for retinal degeneration. Thus one skilled in the art would not have

been motivated to combine the teachings of Wheeler et al., Sallman et al and Wen et al. to produce an ophthalmic composition for treatment of retinal degeneration comprised of brimonidine and growth factors, such as that disclosed in Applicant's rejected Claims 19, 20, 23 and 24. Applicants respectfully request that these rejections be withdrawn.

Applicants request that the application as amended be reconsidered. Should the Examiner have any questions or suggestions, the undersigned respectfully requests a telephone conference at (561) 671-3665.

Respectfully submitted,



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